REMARKS

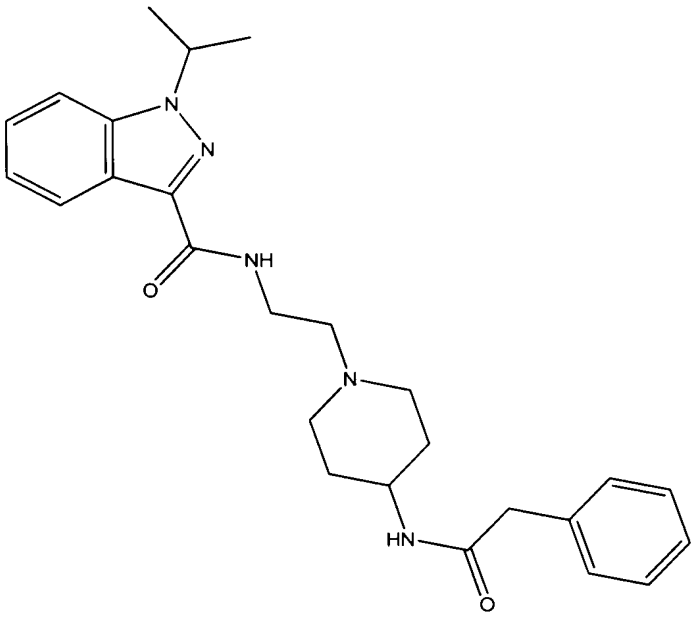
Claims 1-31 and 33-35 are pending in the present application.

At the outset, Applicants wish to direct the Examiner's attention to the fact that Form PTO-892 improperly fails to list Suzuki et al, US 6,096,746. Apparently as a result of a typographical error, Suzuki et al, US 6,096,746, has been entered as US 6,096,476 under the name Yanagida et al. Cursory inspection of US 6,096,476 clearly indicates that the citation of this reference is an error as US 6,096,476 is related to "Direct Drawing Type Waterless Planographic Original Form Plate" and not indazolamides as claimed. To ensure completeness of the record, Applicants **submit herewith** a Form PTO-1449 listing Suzuki et al, US 6,096,746.

The rejection of Claims 1-35 under 35 U.S.C. 103(a) over Catlow et al (US 5,654,320) in view of Suzuki et al (US 6,096,746) and Schaus et al (J. Med. Chem. 1998) is respectfully traversed.

The Examiner cites Catlow et al as disclosing 5-HT4 receptor binding compounds for treating gastrointestinal disorder and specifically referred to the compound of column 14, Example 26.

Example 26 of Catlow et al, N-[2-(4-benzylcarbonylamino-1-piperidinyl)ethyl]-1-(2-propyl)-1H-indazole- 3-carboxamide, has the formula:



The Examiner alleges that the compound of Example 26 of Catlow et al is "structurally very close to the claims" citing the species of Claim 8, N((1-(2-(4-nitrophenyl)ethyl)-4-piperidinyl)methyl)-1H-indazole-3-carboxamide hydrochloride.

The Examiner then alleges that the compound of Claim 8 only differs from the compound of Example 26 of Catlow et al by (i) one methylene linker between the indazolyl and the piperidinyl ring, (ii) the rotation of the piperidinyl ring, and (iii) the reverse amidomethyl linkage.

The Examiner then alleges that:

- difference (i) is an optional choice for such compounds in view of Suzuki et al., column 54-55 examples 18 and 19,

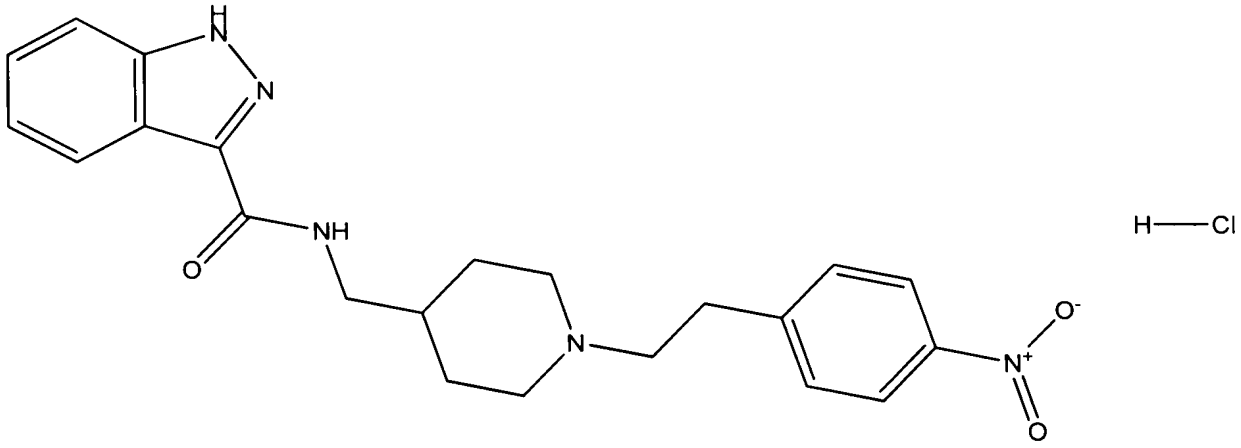
- difference (ii) is an optional choice for the class of 5HT4 receptor binding in view of Schaus et al., page 1948 table 3 vs. page 1950 table 5, and

- difference (iii) is an optional choice for such compounds in view of Schaus et al., page 1948 compound 19j vs. page 1950 compound 23j, both having potent binding activity as

stated on page 1948 right column last four lines and page 1951 right column 2nd paragraph last 10 lines.

Applicants disagree with these allegations by the Examiner and the ultimate allegation of obviousness.

Contrary to the Examiner's allegation, the structure of N((1-(2-(4-nitrophenyl)ethyl)-4-piperidinyl)methyl)-1H-indazole-3-carboxamide hydrochloride is:



Thus, the linker between the piperidinyl ring and the phenyl ring is not an amidomethylene linker as alleged by the Examiner, but rather is an ethylene linkage ($-CH_2CH_2-$). Accordingly, difference (iii) is not simply a matter of reversing the amidomethylene linkage, but of substituting such linkage with an ethylene linkage.

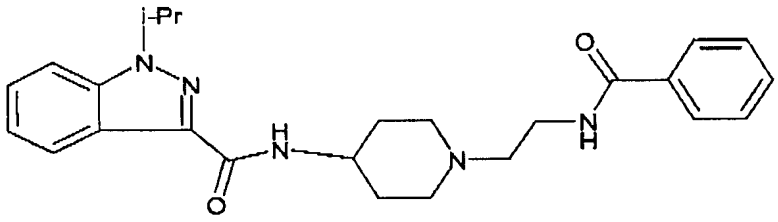
Furthermore, Applicants submit that Catlow et al, Suzuki et al, and Schaus et al disclose 5HT4 receptor binding compounds for treating gastrointestinal disorders. None of the references disclose or suggest employing the disclosed compounds as analgesic. Further, none of the references disclose or suggest to modify the disclosed compounds with the reasonable expectation of finding novel analgesic compounds.

As for difference (i), Suzuki et al do not disclose or suggest that the difference of a methylene linker is an optional choice. When comparing compounds 23, 18 and 19 of Table

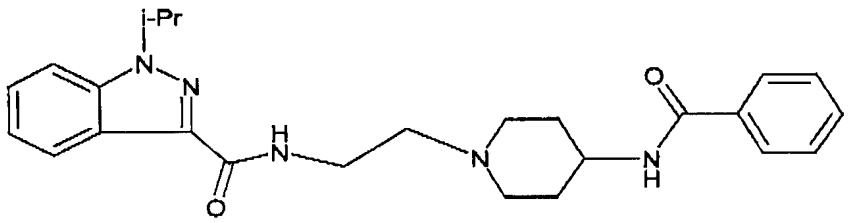
1 (having 0, 1, or 2 methylene groups as linker between the amido group and the piperidinyl ring) there is a clear indication that the higher activity is connected with m=2, followed by m=0 and last by m=1. On the contrary, when comparing compounds 22, 7, and 8 the higher activity is connected with m=1, followed by m=0 and last m=2. So, this confirms what is the actual knowledge of the skilled artisan in pharmaceutical chemistry, that is that a simple change can have different effect depending from the actual and specific molecular structure under consideration.

With respect to difference (ii) Schaus et al do not disclose or suggest that the rotation of the piperidinyl ring is an optional choice. In particular, it is not true that compound 19j and compound 23j are described in Schaus et al as having both "potent binding activity" as stated by the Examiner. Schaus et al literally define only compound 19j a "potent 5-HT4 receptor antagonist" (see page 1948 right column last four lines) while compound 23j is only mentioned as a "5-HT4 receptor antagonist" without the adjective "potent". As a consequence, the rotation of the piperidinyl ring may influence the activity.

A comparison of compound 19j with compound 23j is not an objective comparison for arguing that the rotation of the piperidinyl ring is an optional choice, because compounds 19j and 23j have other structural differences that can influence their activity, as shown below:



19j



23j

In particular, compound 19j has no methylene groups linking the indazolamido ring to the piperidinyl ring, while has two methylene groups linking the piperidinyl ring to the benzamido ring. On the contrary compound 23j has two methylene groups linking the indazolamido ring to the piperidinyl ring, while has no methylene groups linking the piperidinyl ring to the benzamido ring.

The Examiner has alleged that the substitutions on the phenyl ring are *prima facie* obvious in view of Schaus et al at page 1944. However, on page 1944 only compounds 2 cisapride and 7, RS100235 have substitutions on the phenyl ring. However, these compounds are structurally different from the compounds of the present invention, in particular RS100235, and on page 1943, last paragraph it is stated that cisapride is not particularly potent for 5-HT4 receptors and has high affinity for other receptors. So, even if substitution of a phenyl ring are well known to the skilled artisan, there is no suggestion in Schaus et al to provide such substitutions.

With the foregoing deficiencies in the Examiner's allegations in mind, Applicants direct the Examiner to *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) in which the Court of Appeals for the Federal Circuit clearly state that in order to find a *prima facie* case of unpatentability, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required (*Takeda* at 1174, citing *In re Jones*, 958 F.2d 347, 21 USPQ2d

1941 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990); *In re Grabiak*, 769 F.2d 729, 226 USPQ 870 (Fed. Cir. 1985); *In re Lalu*, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984)).

Moreover, as clearly stated by *Takeda* at 1174, the Court squarely addressed the test for *prima facie* obviousness enunciated by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 [82 USPQ2d 1385](2007) in the context of chemical compounds:

> That test for *prima facie* obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.[2] While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight"to an obviousness inquiry. *Id.* Thus, ***in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.*** (*emphasis added*)

Applicants submit that the present invention is not obvious in view of Catlow et al, even when combined with Suzuki et al and Schaus et al, as this reference fails to provide the requisite reason that would have led a chemist to modify the compounds disclosed therein in the manner necessary to arrive at the claimed compounds. Thus, Catlow et al, even when combined with Suzuki et al and Schaus et al, fails to support even a *prima facie* case of obviousness.

In view of the foregoing, Applicants request withdrawal of this ground of rejection.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

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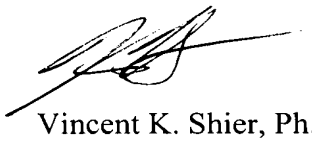
Norman F. Oblon



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